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Monitoring of pharmaceutical processes with image analysis: direct and indirect approaches

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1. Introduction

Formulating poorly water soluble active pharmaceutical ingredient (API) in an amorphous form is a promising approach in increasing water solubility and bioavailability. However poor physical stability leads to nucleation and crystal growth over time.

Estimation of the extent of nucleation and crystal growth in the early formulation development provides insight into the stabilizing effect of the excipients on the API. It can be done using polarized light microscopy together with image analysis. However, when the API crystallizes out as needles intersecting each other (Fig. 1), the counting and length estimation of the needles becomes very challenging.

In the present study, two methods for estimation of needle shaped crystal nucleation and growth are proposed. The first method presents a direct approach in estimating size and number of needles, and the second method presents an indirect approach for estimating nucleation and crystal growth.

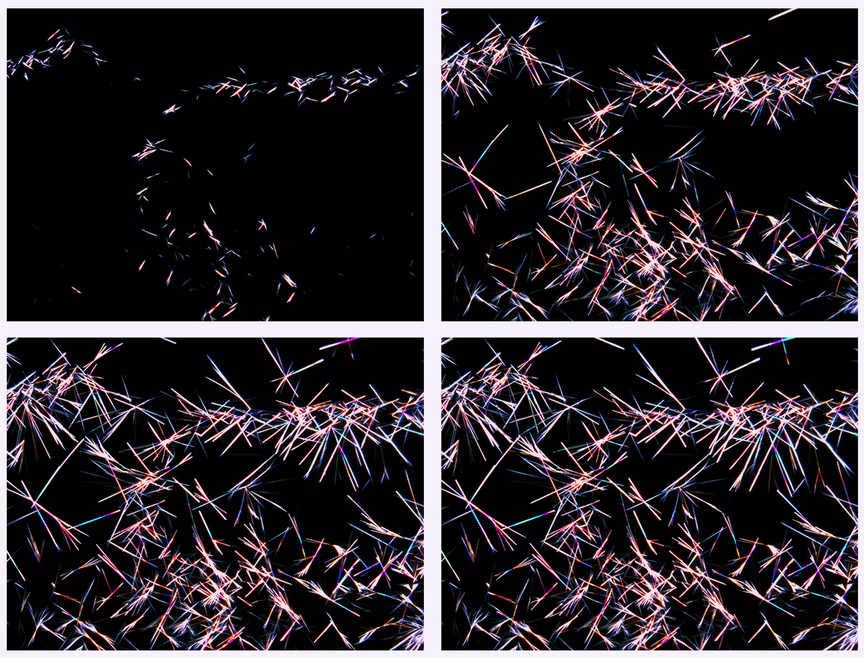

Fig. 1. Microscopic images of API crystallization process

2. Simulated images

In order to be able to validate and compare the methods, an image simulation procedure was developed. For each predefined process specific parameters (number of needles, distribution of their size, curvature, etc.) a series of 500 images was generated where needles are growing from minimum to maximum length.

Bezier cubic splines were used to simulate the needle growth. It allowed to emulate different growth kinetics, e.g. following linear, logarithmic, cubic and sigmoid function. Figure 2 presents four simulated images of the same growth kinetic process with 1000 needles.

Both methods were applied to the generated series and used to predict a relative (in percent of maximum size) length of needles at each process stage. The result was then compared with the true, predefined values.

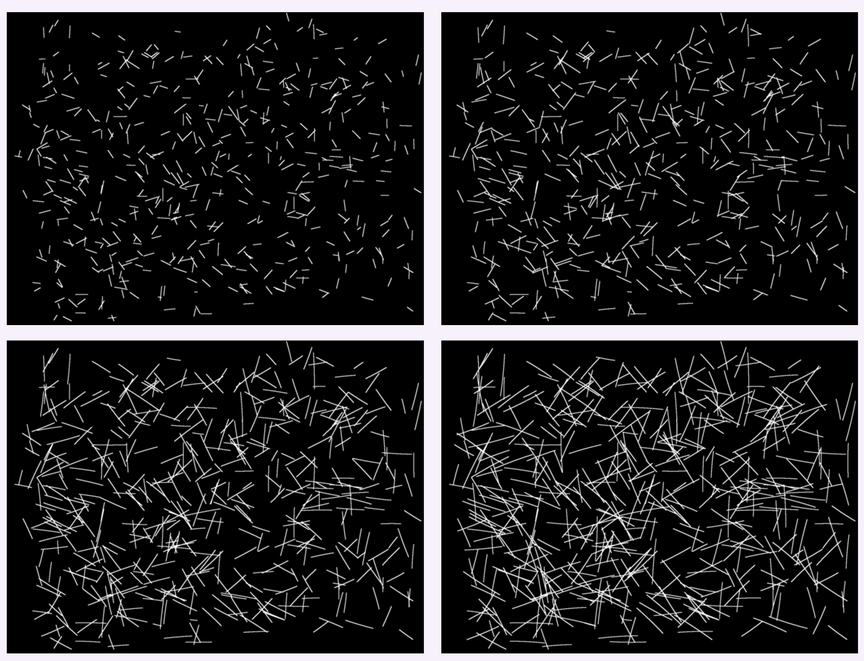

Fig. 2. Simulated images of API crystallization process

3. Methods

Method for direct estimation of needle count and length is based on Radon transformation, which allows to detect lines on noisy image by transforming the image into a parametric space. Each non-zero pixel is represented by a sine curve in the space. Straight lines from the image forms a set of peaks in the parametric space, which can be detected using thresholding procedure or more sophisticated algorithms. Figure 3 (right) shows how Radon transformation works for line detection on a part of a real process image.

The indirect approach utilizes an idea to treat every image as a texture, and use multivariate models for finding relations between textural features and the change in needle length. Angle Measure Technique (AMT) was used to extract textural features for the images, then Principal Component Analysis was applied to AMT features in order to get the relationship. Figure 3 (left) shows how AMT textural features are calculated.

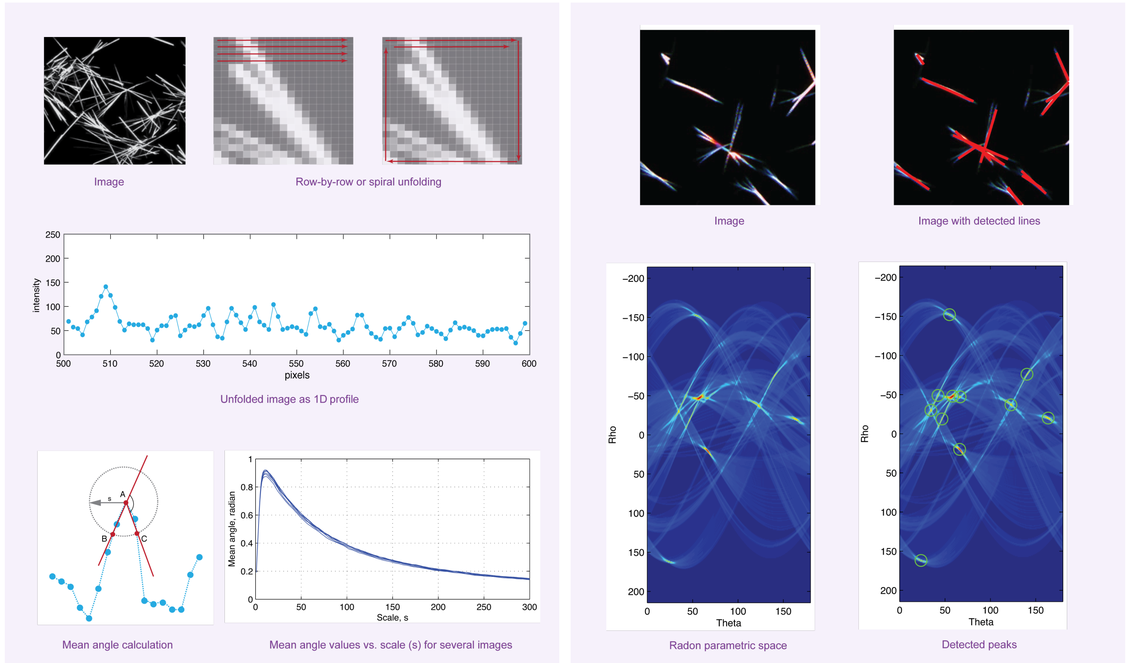

Fig. 3. AMT feature extraction (left) and Radon line detection (right) schemes

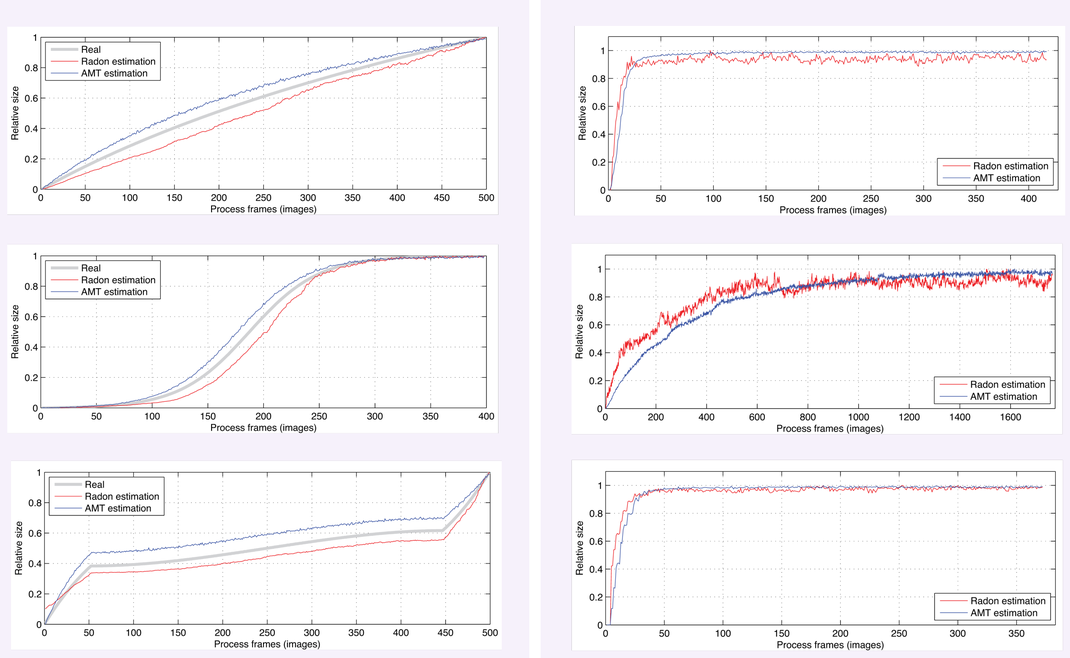

Fig. 4. Results of monitoring particle growth for simulated (left) and real (right) process images

4. Results

Both methods were applied to the simulated series with different growth functions as well as to real process images. In the latter case frames of videos of the crystallization processes were recorded using polarized light microscopy. Some of the results are presented in Figure 4. In the case of AMT, normalized score values of the first principal components were used as a size estimator.

It can be seen that both methods performs well, and follow the needle length growth kinetic curve quite close (Fig 4). Computationally AMT is almost 10 times faster, however can not estimate the needles in terms of absolute length. In conclusion, AMT can be considered as a fast formulation ranking and comparison method suitable for early stage formulation screening, while Radon based approach provides absolute estimation of nucleation and needle growth.

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